Copeptin in the Diagnosis of Diabetes Insipidus

TO THE EDITOR: In their study of the value of copeptin for diagnosing diabetes insipidus, Fenske et al. (Aug. 2 issue)[1] overlook two possible methodologic flaws. First, some of their patients appear to have had an element of a solute diuresis. For example, among patients with primary polydipsia, the product of the baseline median urine osmolality (408 mOsm per kilogram) and a urine volume of 4 liters per day or more indicates that in some patients the daily urine solute load was more than 1600 mOsm, which greatly exceeds the normal value (approximately 10 mOsm per kilogram per day).[2,3] Second, the water-deprivation test was incomplete. The goal is to raise the serum sodium and endogenous vasopressin levels sufficiently to induce maximal urine concentration, as shown by stability of the urine osmolality.[4,5] This critical step was omitted. Therefore, we cannot know whether the stimulus was adequate and whether restricting water longer would have changed the results. That the serum sodium levels were notably higher after the administration of hypertonic saline than after water deprivation suggests that it might have. Thus, the authors' conclusion that measurement of hypertonic saline–stimulated copeptin is superior to water-deprivation testing seems premature.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: I was disappointed in the article by Fenske et al., which seemed to claim that the assay of plasma copeptin is the best way to differentiate partial central (pituitary) diabetes insipidus from primary polydipsia. Limitations on length for letters to the editor preclude a complete listing of the many apparent oddities and deficiencies in the data and conclusions. Suffice it to note that the copeptin values during infusion of 3% saline are not expressed relative to the concurrent plasma sodium level. Therefore, the interpretation fails to take into account the large differences in the level of osmotic stimulation between the two groups. In addition, the accuracy of the interpretation is based on the opinion of experts and not on the effect of a closely monitored trial of desmopressin therapy (the most reliable standard). Most troubling of all, the diagnosis made from the copeptin data correlates poorly with the presence or absence of the posterior pituitary "bright spot" on magnetic resonance imaging. When plasma arginine vasopressin is used for differential diagnosis, the bright spot is always present in primary polydipsia but absent or small in partial pituitary diabetes insipidus.[1]

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TO THE EDITOR: The diagnostic and prognostic yields of copeptin, a surrogate biomarker of arginine vasopressin secretion, are currently investigated in various disorders linked to arginine vasopressin regulation, including heart failure, sepsis, or the metabolic syndrome.[1] More specifically, patients with autosomal dominant polycystic kidney disease (ADPKD), which has a prevalence of 1 in 400 to 1000 live births, show significantly higher plasma copeptin levels than controls.[2] Plasma copeptin levels independently correlate with ADPKD progression.[3] Copeptin secretion after hypertonic saline stimulation in patients with ADPKD is unknown.

In the study involving 144 patients with hypotonic polyuria, Fenske et al. elegantly show that

measuring plasma copeptin after infusion of 3% saline over a period of 3 hours has greater diagnostic accuracy than 17-hour water deprivation. This test will probably replace the water-deprivation test in the diagnostic workup of polyuria, with a copeptin cutoff level of more than 4.9 pmol per liter.[4] It is not clearly mentioned that this cutoff value is a delta — that is, a change in the plasma copeptin level at a plasma sodium level of 147 mmol per liter or more versus baseline. It would have been relevant to provide pretest copeptin levels according to subgroup. Indeed, specific conditions, such as ADPKD, are essentially characterized by an increased plasma copeptin level, a fact that may pragmatically skew the diagnostic yield of copeptin measurement after hypertonic saline stimulation in the challenging context of hypotonic polyuria.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Spital correctly notes that solute excretion determines free-water excretion. However, solute diuresis as a main cause of chronic polyuria is unlikely, because enrollment required hypotonic polyuria during screening diagnostics and exclusion of patients with glucosuria and electrolyte diuresis. The given baseline urine osmolality was assessed with the use of spot urine samples obtained the morning of the testing day, at which point most patients had been fluid-restricted overnight.

It is possible that a more extended dehydration period might have affected the diagnosis derived from the indirect test in individual patients. However, the 17-hour fluid deprivation is well in line with the previously reported dehydration periods required to induce maximal urine concentration (8 to 18 hours)[1] and confirms diagnostic inferiority of the indirect water-deprivation test as compared with the direct test of arginine vasopressin function.[2] Importantly, because this 17-hour water-deprivation protocol was already cumbersome for patients, the test involving the infusion of 3% saline is arguably more reliable and convenient.

A therapeutic trial with desmopressin alone, as suggested by Robertson, is neither a good nor an accepted standard to differentiate diabetes insipidus from primary polydipsia. Taking the treatment response into account — as we did in our diagnostic reference standard — enables high diagnostic accuracy.

Robertson's second point, regarding the presence of a bright spot in all patients with primary polydipsia, also lacks evidence. Although the diagnostic accuracy of the bright spot has never been prospectively investigated, an age-related absence of a pituitary bright spot was previously reported in up to 20% of normal healthy humans,[3] and other studies have shown the presence of a bright spot in patients with clinical evidence of central diabetes insipidus.[4] Our data provide evidence that neither its specificity nor its sensitivity is high enough to use the presence or absence of a pituitary bright spot as a diagnostic measure.

Preserving tradition,[2] we show the plasma copeptin levels during the infusion of 3% saline relative to serum sodium levels in Figure S2 in the Supplementary Appendix (available with the full text of our article at NEJM.org). More importantly, given the feasibility of the test interpretation in the clinical routine, the test involving the infusion of 3% saline was deliberately designed to nearly equalize the level of osmotic stimulation in all patient groups (Fig. S4 in the Supplementary Appendix).

We thank Mekahli and Jouret for mentioning the value of copeptin as a prognostic surrogate in patients with ADPKD. With respect to the diagnostic application of copeptin in hypotonic polyuria, it is important to clarify that pretests according to subgroup had been provided[5] and were

prospectively validated; this confirmed a stimulated copeptin level of 4.9 pmol per liter as an absolute cutoff value, not a delta.

Patients with ADPKD generally have a form of nephrogenic diabetes insipidus, which may be clinically masked in patients receiving dialysis. For the probably very rare condition of suspected central diabetes insipidus in a patient with ADPKD, no data are yet available.

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Since publication of their article, the authors report no further potential conflict of interest.

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